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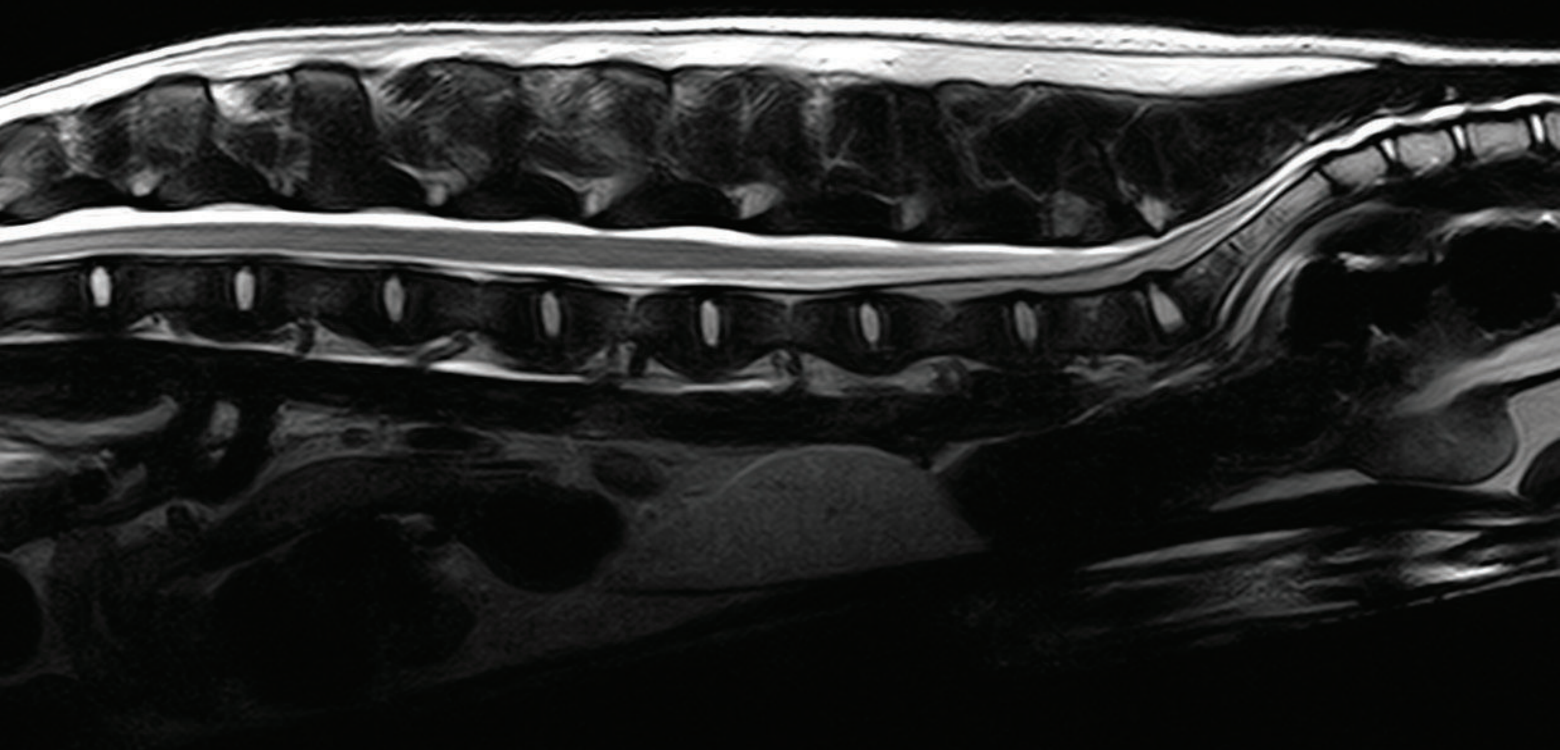

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Prevalence of Unilateral and Bilateral Deafness in Border Collies and Association with Phenotype

Simon Platt, Julia Freeman, Alberta di Stefani, Lara Wieczorek, and William Henley

Background: Congenital sensorineural deafness (CSD) occurs in Border Collies, but its prevalence and inheritance are unknown. This study estimated the prevalence of CSD in Border Collies and investigated its association with phenotypic attributes linked to the merle gene, including coat pigmentation and iris color.

Hypothesis: Deafness in Border Collies is associated with pigmentation patterns linked to the merle gene.

Animals: A total of 2597 Border Collies from the United Kingdom.

Methods: A retrospective study of Border Collies tested, during 1994–2002, by using brainstem auditory evoked responses. Associations between deafness and phenotypic attributes were assessed by using generalized logistic regression.

Results: The prevalence of CSD in puppies was estimated as 2.8%. The corresponding rates of unilateral and bilateral CSD were 2.3 and 0.5%, respectively. Adjustment for clustering of hearing status by litter reduced the overall prevalence estimate to 1.6%. There was no association between CSD and sex ($P = .2$). Deaf Border Collies had higher rates of merle coat pigmentation, blue iris pigment, and excess white on the head than normal hearing Border Collies (all $P < .001$). The odds of deafness were increased by a factor of 14 for Border Collies with deaf dams, relative to the odds for dogs with normal dams ($P = .007$), after adjustment for phenotypic attributes.

Conclusions and Clinical Importance: Associations between CSD and pigmentation patterns linked to the merle gene were demonstrated for Border Collies. Evidence for an inherited component to CSD in Border Collies supports selective breeding from only tested and normal parents to reduce the prevalence of this disease.

Key words: Brainstem auditory evoked response; Congenital deafness; Hearing; Merle; Neurophysiology.

Deafness in dogs is routinely and objectively assessed by using brainstem auditory evoked responses (BAER)[1–3] BAER testing provides information about the functional state of the peripheral and brainstem components of the auditory nervous system, and can be defined as the electrical response of the auditory pathway to a series of auditory stimuli.[1–3] The BAER test has been shown to be a reliable method of detecting auditory problems caused by otologic disease in dogs and to give a quick, noninvasive and objective assessment of an individual's hearing status.[1,2,4,5]

Dogs are tested from 6 weeks of age, because cochlear receptor-cell development is complete by this time.[3–8] Dogs who are deaf by this age are considered to be affected with congenital sensorineural deafness.[1,4,6,7] Although most studies of congenital deafness have formerly been carried out on the Dalmatian,[5,8–17] the prevalence of congenital deafness in the Bull Terrier, English Setter, Pointer, Catahoula Leopard dog, Whippet, Australian Cattle dog, Jack Russell Terrier, Dachshund, and English Cocker Spaniel has also been evaluated.[5,17–19] In fact, more than 60 breeds of dog have now been identified as suffering from congenital sensorineural deafness,[17] including the Border Collie. Most of these breeds carry the alleles s^p for piebald spotting or s^w for extreme white piebald coloring; both of these alleles are thought to be carried by the Border Collie.[17] Border Collies also carry the dominant merle gene M,[17] another pigmentation allele associated with deafness.

An association between blue eye color and congenital deafness has been recognized for over 100 years.[17] Studies carried out on Dalmatians with blue eyes showed that there was an increased prevalence of congenital deafness in dogs with one or more blue eyes.[14,17] The lower prevalence of congenital deafness in Dalmatians in the UK, where blue-eyed dogs are not allowed for breeding, seems to support this.[5,8–10,13] Blue eyes are accepted in the breed standard for Border Collies with a merle coat color.

The aims of this study, which is part of a larger investigation into congenital deafness in Border Collies, were the following: (1) to report the prevalence and sex distribution of unilateral and bilateral deafness in Border Collies by using BAER and clinical observations; (2) to quantify how deafness varied with other phenotypic attributes, including coat pigmentation and iris color; and (3) to investigate relationships between parental and offspring hearing status.

Materials and Methods

Dogs

The BAER test results of 2597 Border Collies presented to the Animal Health Trust (1994–2002) for assessment of their hearing status were evaluated. Of these, 2303 were puppies aged 9 weeks old or younger, and 294 were more than 9 weeks old. An additional 20 dogs who were tested with BAER and found to have impaired hearing were excluded from this study.

All dogs were purebred, although not all were registered with the UK Kennel Club. Most puppies were tested, at approximately 6 weeks of age, with their litter mates. Many of the adult dogs were tested before being used for breeding if they had not been tested as a puppy, although some were tested because the owner had become suspicious that the dog had abnormal hearing.

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In most cases, entire litters were tested, unless puppies had died at birth, died subsequently from failure to thrive, been killed accidentally by the dam, or been euthanized because of a birth defect, eg, cleft palate.

Phenotype Recording

Phenotypic markers were recorded, which included coat color, sex, and iris color. In addition, dogs with excess white pigmentation (subjectively estimated at more than 50% of the head) were noted.

Coat color was recorded as one of the following possibilities: black and white; black, white, and tan; red and white; red, white, and tan; blue and white; blue, white, and tan; blue merle; red merle; predominantly white; and any other color. For the purposes of analysis, coat color was classified according to the dominant color: black, blue, red, or merle. Dogs who had white as the dominant color were allocated to the color group of their existing pigmented areas. Sex was recorded as male or female; if an adult had been neutered, then this was also recorded. Iris color was recorded as 2 brown eyes, 1 blue eye, or 2 blue eyes; if a dog's iris was partially blue, then this was also recorded.

Testing Protocol

Puppies were always tested conscious, although they often naturally became drowsy after a period of wakefulness. Adult dogs were often tested without sedation, but if necessary, a light sedation that consisted of 2–5 μg/kg meditomidine hydrochloride[a] and 0.1–0.2 mg/kg butorphanol tartrate[b] was administered. After the procedure, if required, atipamezole hydrochloride[c] was given at a dose of 10–25 μg/kg, as needed, intravenously.

Recording was carried out by using 12-mm stainless steel subdermal needle electrodes. The reference electrode was placed at the vertex, and the ground electrode was inserted over the occiput. The recording electrode was placed just rostral to the tragus of the ear being tested. This was then moved to the corresponding position on the contralateral side before testing the other ear, as has been described.[3] The right ear was tested first, followed by the left ear.

Electrodiagnostic Equipment. Brainstem auditory evoked responses were recorded by using a standard electrodiagnostic machine.[d] The sweep duration was set at 10 ms, amplifier sensitivity at 20 μV per division, and display gain at 20× magnification (ie, 1 vertical division on the screen = 1 μV). The filters were set with a low frequency cutoff setting of 100 Hz and a high frequency setting of 2 kHz. This bandwidth was chosen because it gave the clearest, most detailed BAER waveform.

Recording Parameters. Rarefaction clicks of 100 μs duration were presented at 50 dB nHL via an unshielded audiometric headphone,[e] held against the opening of the ear. Data were obtained at a click rate of 20/s, which gave a good waveform in the shortest time. At a stimulus rate greater than 20 Hz, some of the detail of the waveform is lost; 512 responses were signal averaged to eliminate artefact. If no response was elicited at 50 dB, then the test was repeated at 80 dB, and if this was also unsuccessful, then again at 100 dB. To eliminate crossover recordings from a functional contralateral ear, white noise was delivered into the other ear, at 20 dB lower than the stimulus, to mask the stimulus from the ear being stimulated. The procedure was repeated for the opposite ear.

Data Classification. Animals were classified as deaf when no recognizable BAER waveform was obtained at even the highest stimulus intensity, unilaterally deaf if only 1 ear failed to produce a trace, and bilaterally deaf if neither ear produced a trace.

Statistical Analysis. Prevalence of deafness was estimated from the BAER data for puppies. Dogs who were tested after 9 weeks of age were excluded from the prevalence estimation to reduce selection bias. Associations between deafness and other attributes, including coat color, iris color, and parental hearing status, were tested by using standard methods for contingency tables.[20] In this approach, a contingency table is formed by cross-classification of the deafness categories (eg, deaf and normal) by the levels of the explanatory factor (eg, male and female sexes). The chi-square test with the Yates correction was used to test for associations when less than 25% of the cells in the contingency table had expected counts of less than 5. When this condition was not satisfied, associations were tested by using the Fisher exact test. Separate analyses were conducted for Border Collies by age group (9 weeks or under and over 9 weeks old) and for both age groups combined. The significance level for all statistical tests was set as 0.05.

BAER data on the 2,597 tested Border Collies were merged with the Kennel Club's pedigree database of 33,550 registered Border Collies in the UK. The composite database was used to assess associations between deafness and the hearing status of parents and close relatives. Eleven dogs with inconsistent or duplicate Kennel Club registration codes were excluded from the analysis (but not from the preliminary assessment of phenotypic associations).

Generalized logistic regression was used to model the relation between overall deafness and other attributes [8,21] This enabled assessment of the combined effects of phenotypic attributes (coat color, iris color) and parental hearing status on the rate of deafness in Border Collies. The generalized logistic regression models included a random effect term for the litter to account for clustering of hearing status by litter. Litters were defined to be unique mating combinations of sires and dams. The identity of one or both of the sire and the dam was missing for 124 of the tested Border Collies. These dogs were considered as a single pseudo-litter for the purposes of the analysis.

The generalized logistic regression models were fitted by using maximum likelihood estimation.[21] Fixed effects were selected for inclusion in the models by using a backward elimination procedure. Variables were retained in the model if they significantly reduced model deviance (likelihood ratio chi-square, $P < .05$). Biologically meaningful 2-way interaction terms were tested between all main effects variables. The significance of the litter variance component was assessed by using a likelihood ratio test. Intraclass correlation coefficients for the litter effect were calculated by using a standard approximation method based on latent variables.[22] This assumes that deafness is the result of an underlying latent process after a continuous logistic distribution, with a mean of 0 and a variance of $\pi^2/3$.

The preliminary analyses provided estimates of the prevalence of deafness by assuming statistical independence of the tested Border Collies with respect to hearing status. These estimates did not take into account the possibility of clustering by litter but were included to enable comparison with other similar studies.[5,13,17] The possible impact of such litter effects was explored by using the parameter estimates and variance-covariance matrices of the univariable generalized logistic regression models to calculate additional estimates of the prevalence of deafness (and approximate 95% confidence intervals) for different subsets of the tested Border Collies. All analyses were carried out by using commercially available software.[f]

Results

Overall Prevalence

Among the 2,597 tested Border Collies, 2,481 (95.5%) had normal BAER, 60 (2.3%) were unilaterally deaf and 56 (2.2%) were bilaterally deaf. The percentages of

Table 1. The observed number and percentage of deafness categories in Border Collie puppies (≤9 weeks), adults (≥9 weeks), and all 2,597 tested Border Collies.

Deafness Category	Puppies No.	Puppies Rate	Adults No.	Adults Rate	Overall No.	Overall Rate
Normal	2,239	97.2	242	82.3	2,481	95.5
Overall deafness	64	2.8	52	17.7	116	4.5
Unilateral	53	2.3	7	2.4	60	2.3
Bilateral	11	0.5	45	15.3	56	2.2
Total	2,303	100%	294	100%	2,597	100%

Table 2. The observed number and percentage of deafness categories in female and male Border Collie puppies.[a]

Deafness Category	Female No.	Female Rate	Male No.	Male Rate
Normal	1,061	97.3	1,178	97.2
Overall deafness	30	2.7	34	2.8
Unilateral	24	2.2	29	2.4
Bilateral	6	0.5	5	0.4
Total	1,091	100%	1,212	100%

[a] Chi-square = 0.32, df = 2, $P = .9$.

unilateral and bilateral deafness differed between puppies and adult dogs (Table 1). In particular, the percentage of bilateral deafness was much higher among adult dogs (15.3%) than among puppies (0.5%), reflecting the nonrandom selection of adult dogs for testing. The overall prevalence of congenital deafness was estimated from the test results for puppies as 2.8%. The corresponding prevalences of congenital unilateral and bilateral deafness were 2.3 and 0.5%, respectively.

Association with Sex. The prevalence of overall congenital deafness (estimated from puppies only) was 2.7% among females and 2.8% among males (Table 2). There was no association between deafness status and sex for puppies (chi-square test, $P = .9$) or adults (Fisher exact test, $P = .7$).

Associations with Phenotypic Attributes. The percentage of deaf (unilateral and bilateral combined) and normal hearing Border Collies by the phenotypic attributes dominant coat color (black, blue, red, merle, or white), iris color (2 brown, 1 blue/partial blue, or 2 blue), and excess white pigmentation, separately for puppies, adults and all 2,597 tested dogs is shown in Table 3. The merle category included both red merle (37 dogs) and blue merle (123 dogs). Deaf Border Collies had higher observed rates of excess white or merle coat pigmentation and blue iris pigmentation than normal hearing Border Collies, with the difference being greater among puppies than adults. Significant associations with deafness were found for coat pigmentation varieties linked to the merle gene across all age categories (Table 4). No differences in deafness percentage were found between dogs with red and blue merle coats ($P = .24$, for all 2,597 tested Border Collies). Associations between deafness and the phenotypic attributes of iris color and excess white on the head were significant among puppies and all 2,597 tested Border Collies but not among dogs tested after 9 weeks (Table 4).

Association with Parental Hearing Status. If deafness in Border Collies is affected by the hearing status of parents or other ancestors, the prevalence should be

Table 3. The percentage of Border Collies from each deafness category split by the phenotypic attributes, coat color, iris color, and white pigmentation, for puppies (≤9 weeks), adults (≥9 weeks), and all 2,597 tested Border Collies.

	Puppies				Adults				Overall			
Phenotype	No.	% of Total N = 2,303	% of Normal Hearing N = 2,239	% of Deaf N = 64	No.	% of Total N = 294	% of Normal Hearing N = 242	% of Deaf N = 52	No.	% of Total N = 2,597	% of Normal Hearing N = 2,481	% of Deaf N = 116
Coat color[a]												
Black	1,704	74.0	74.5	56.3	220	74.8	75.6	71.2	1,924	74.1	74.6	62.9
Red	324	14.1	14.1	14.1	44	15.0	16.1	9.6	368	14.2	14.3	12.1
Blue	119	5.2	5.2	4.7	10	3.4	3.7	1.9	129	5.0	5.0	3.5
Merle	145	6.3	5.8	25.0	18	6.1	4.1	15.4	163	6.3	5.6	20.7
Iris color												
2 Brown	2,158	93.7	94.6	64.1	276	93.9	95.0	88.5	2,434	93.7	94.6	75.0
1 Blue	109	4.7	4.3	20.3	10	3.4	2.9	5.8	119	4.6	4.2	13.8
2 Blue	36	1.6	1.2	15.6	8	2.7	2.1	5.8	44	1.7	1.3	11.2
White pigments												
No	2,261	98.2	98.9	73.4	292	99.3	99.6	98.1	2,553	98.3	99.0	84.5
Yes	42	1.8	1.1	26.6	2	0.7	0.4	1.9	44	1.7	1.0	15.5

[a] Frequencies for 11 dogs with other dominant coat colors are not shown; dogs with white as the dominant coat color were allocated to the color group of their existing pigmented areas.

Table 4. Significance testing of differences in deafness prevalence by coat pigmentation, iris color, and excess white pigmentation on the head for puppies (≤9 weeks), adults (≥9 weeks) and all 2,597 tested Border Collies.

Phenotype	Comparison	Age Category	N[a]	Deaf[b]	Chi-square Test, P	Fisher Exact Test, P[c]
Coat color	Black/blue/red/other versus merle	Puppy	2,303 (2,158/145)	64 (48/16)	<.001	<.001
		Adult	294 (276/18)	52 (44/8)	.002	.006
		All ages	2,597 (2,434/163)	116 (92/24)	<.001	
Iris color	2 Brown versus 1 blue or partial blue versus 2 blue	Puppy	2,303 (2,158/109/36)	64 (41/13/10)	<.001	<.001
		Adult	294 (276/10/8)	52 (46/3/3)	.183	.126
		All ages	2,597 (2,434/119/44)	116 (87/16/13)	<.001	
Excess white	No versus yes	Puppy	2,303 (2,261/42)	64 (47/17)	<.001	<.001
		Adult	294 (292/2)	52 (51/1)	.230	.323
		All ages	2,597 (2,553/44)	116 (98/18)	<.001	<.001

[a] N = total number of dogs; numbers in brackets refer to numbers of dogs in 2 comparison groups (in same order as in "comparison" column)
[b] Deaf = total number of deaf dogs; numbers in brackets refer to numbers of deaf dogs in 2 comparison groups (in same order as in "comparison" column)
[c] P values shown for Fisher exact test where 1 or more of the cells in the 2 × 2 contingency table have expected values less than 5.

lower in dogs with parents having normal hearing. The rate of deafness was significantly higher among the offspring of unilaterally or bilaterally deaf dams (10.0%) than among the offspring of normal hearing dams (2.6%; Fisher exact test, P = .01). There were too few tested Border Collies with deaf sires for direct assessment of the effect of the sire's hearing status. However, some of the untested sires will have been deaf, so an indirect assessment was made by comparing the hearing status of offspring from tested normal sires with the hearing status of offspring from untested parents. The rate of deafness was 3.4% in Border Collies with sires that tested normal and 7.2% in Border Collies with untested sires (chi-square test, P < .001). More generally, the rate of deafness was between 2.5 and 4% if at least 1 of the dog's parents and grandparents had tested normal and it increased to more than 8% if at least 1 parent and 1 grandparent were untested. The rate of deafness was significantly lower when both parents were tested normal, than when both parents were untested (2.7 versus 12.0%, respectively; chi-square test, P < .001).

When considering puppies alone, the rate of deafness was 2.2% among the offspring of normal hearing dams and 10.0% among the offspring of deaf dams (Fisher exact test, P = .013). The prevalence of deafness was also lower among puppies with normal hearing dams (2.2%) than among puppies with untested dams (4.2%; chi-square test, P = .015). There was no corresponding difference in deafness prevalence between dogs with normal hearing sires and those with untested sires (chi-square test, P = .8).

Generalized Logistic Regression. Generalized logistic regression was used to model the relation between overall deafness (unilateral or bilateral) and the explanatory variables for phenotypic attributes and parental hearing status among all tested Border Collies. Dam's hearing status was treated as an unordered categorical variable with 3 levels: deaf, untested, and tested normal. Sire's hearing status was treated as a binary variable with categories normal and untested/deaf, because of the low number of deaf sires (n = 4). A summary of the univariable logistic models is shown in Table 5. Dam's hearing status, coat color, iris color, and presence of excess white pigment were all significantly associated with deafness (P < .05), consistent with the results of the contingency table analysis. However, unlike in the exploratory analysis, the effect of sire's hearing status was not significant after adjusting for clustering by litter (P = .14).

The selected multivariable logistic regression model for overall deafness is shown in Table 6. The presence of excess white pigment on the head and merle, because

Table 5. Summary of univariable generalized logistic regression models for overall deafness among all tested Border Collies, showing the odds ratios and associated 95% confidence intervals for each explanatory variable.

Explanatory Variable	Sample Size	Odds Ratio	95% Confidence Interval	P Value
Sex				
Male	1,308	0.75	0.49–1.15	.185
Female	1,278	1.00		
Coat color				
Merle	163	4.94	2.51–9.74	<.001
Other	2,423	1.00		
Iris color				
2 Blue	44	17.55	6.22–49.49	<.001
1 Blue	119	5.07	2.45–10.53	<.001
2 Brown	2,423	1.00		
Excess white				
Yes	44	42.0	15–117	<.001
No	2,542	1.0		
Dam's hearing status				
Deaf	50	9.25	1.83–46.91	.008
Untested	633	4.03	2.14–7.57	<.001
Normal	1,903	1.00		
Sire's hearing status				
Deaf/untested	740	1.63	0.86–3.10	.137
Normal	1,846	1.00		

Table 6. Multivariable generalized logistic regression model of overall deafness in all tested Border Collies.

Model Term	Sample Size	Parameter Estimate	Standard Error	Odds Ratio	95% Confidence Interval	*P* Value
Intercept		−5.9	0.5			<.001
Coat color						
Merle	163	0.8	0.4	2.3	1.0–5.2	.043
Other	2,423	Referent		1.0		
Iris color						
2 blue	44	2.5	0.6	11.9	3.7–38.3	<.001
1 blue	119	1.0	0.4	2.8	1.2–6.4	.016
2 brown	2,423	Referent		1.0		
Excess white						
Yes	44	3.9	0.5	48.3	16.4–141.9	<.001
No	2,542	Referent		1.0		
Dam's status						
Deaf	50	2.6	1.0	13.8	2.1–90.6	.007
Untested	633	1.8	0.4	6.4	3.0–13.6	<.001
Normal	1,903	Referent		1.0		
Litter effect		4.3	1.3			.001
ICC[a]		57%	8%			

[a] ICC, Intraclass correlation.

the dominant coat color were associated with increases in the odds of deafness by factors of 48 and 2.3, respectively. Iris color was significantly associated with deafness ($P < .001$): the odds of deafness increased by factors of 11.9 and 2.8 for Border Collies with 2 blue eyes and 1 with partial blue eyes, respectively, relative to the odds for dogs with 2 brown eyes. Dam's hearing status was significantly associated with deafness after adjusting for phenotypic attributes ($P < .001$): the odds of deafness were increased by factors of 13.8 and 6.4 for Border Collies with deaf and untested dams, respectively, relative to the odds for dogs with tested normal dams. Sire's hearing status was not significant in the multivariable model ($P = .5$). The generalized logistic regression model provided evidence of significant clustering within litters ($P < .001$ for the variance of the random litter effect). The intraclass correlation for the litter effect was 57% (standard error, 8%).

Similar results were obtained when the multivariable model was developed on puppies only. As before, the phenotypic attributes presence of excess white pigment on the head, merle as the dominant coat color, and at least 1 blue iris were associated with increases in the rate of overall deafness ($P < .001$, $P = .016$, and $P < .001$, respectively). Dam's hearing status was also significantly associated with deafness ($P = .025$): the odds of deafness were increased by factors of 7.3 and 1.9 for Border Collie puppies with deaf and untested dams, respectively, relative to the odds for puppies with tested normal dams.

Estimates of the probability of deafness for Border Collie puppies with particular attributes (defined according to phenotype or parental hearing status), after adjusting for clustering by litter by using generalized logistic regression models with appropriate terms are shown in Table 7. Comparison with the earlier estimates shows that accounting for correlations within a litter has resulted in lower prevalence estimates.

Discussion

In this study, 4.5% of Border Collies exhibited unilateral or bilateral hearing loss, but the rates of deafness varied between puppies and adults, presumably because of nonrandom selection of the latter population. The overall prevalence of congenital deafness among Border Collies in the UK was estimated from the

Table 7. Estimated prevalence and 95% confidence intervals for overall deafness in Border Collies obtained by using the estimates (and the variance-covariance matrix) of the parameters of generalized logistic regression models fitted to the data for puppies only.

Border Collie Category	Percentage	95% Confidence Limits	
		Lower	Upper
All Border Collies	1.6	0.7	2.6
Sex			
Males	1.6	0.6	2.7
Females	1.6	0.5	2.6
Sire's hearing status			
Normal sire	1.6	0.7	2.6
Untested sire	1.5	0.3	2.7
Dam's hearing status			
Normal	1.4	0.6	2.3
Untested	2.5	0.6	4.4
Deaf	8.1	0.0	18.0
Coat color			
Merle	7.9	2.6	13.3
Other	1.4	0.5	2.2
Excess white			
Yes	36.3	17.4	55.3
No	1.1	0.3	1.8
Iris color			
2 Blue	23.9	7.7	40.0
1 Blue	9.3	3.0	15.7
2 Brown	1.4	0.6	2.2

puppies as 2.8%, with 2.3% unilaterally deaf, and 0.5% bilaterally deaf. The sample population was not considered to be biased; litters of dogs were evaluated from all parts of the UK and were assessed as part of a screening program set up for this breed at the institution.

This agrees with studies of other breeds in which the frequency of unilaterally affected animals is generally higher than that of totally deaf animals.[17,23] The breeds with the highest observed prevalence of unilateral and bilateral deafness include the Dalmatian (16.5–29.9%),[8,11,13,14,16,17] Bull Terrier (11.0%),[17] English Cocker Spaniel (7.0%),[17] English Setter (7.9%),[17] and Australian Cattle Dog (14.6%).[17,23]

This study found no association between congenital deafness and sex for puppies or adults. The association between sex and congenital deafness has been inconsistent in other breeds. Several studies have demonstrated a significant association between these variables in Dalmatians with females having a higher prevalence;[8,12,13,24] however, other investigations have found a higher prevalence in males or no significant sex difference at all.[15,17] It has been proposed that selective testing, founder effects and relative geographical restriction effects may have an impact on this inconsistent association.[8,17,23]

Associations with Phenotype

This study demonstrated that deaf Border Collies had higher observed rates of white or merle coat pigmentation and blue iris pigmentation than normal hearing Border Collies. The merle-gene–linked coat pigmentations demonstrated a significantly higher prevalence of deafness across all ages of dog, whereas the association of deafness with iris color was most significant in puppies.

Numerous studies have evaluated phenotypic associations with the presence of deafness in dogs, with most studies looking at coat pigmentation patterns.[17,23] In those breeds, such as the Bull Terrier and English Cocker Spaniel, that have white and nonwhite color variants, deafness is significantly more prevalent in the white phenotypes.[4,17] In Dalmatians, the presence of a "patch," a visible pigmented area of hair present at birth, is significantly associated with congenital deafness.[17,23] It seems that "patched" Dalmatians are less likely to be deaf than unpatched.[5,15,17] Border Collies in this study with an excess of white on the head were significantly more likely to be deaf.

The positive association between iris coloration and deafness demonstrated in Border Collies is in agreement with many other studies in which blue eyes are significantly associated with congenital deafness.[5,10,13–15,17]

It has been proposed that the association of congenital deafness with coat color is related to the 3 different recessive alleles of the *S* locus.[23] This locus affects the distribution patterns of pigmented and nonpigmented areas of the body; other genes determine the actual color of the pigmented areas.[23] The *S* locus has at least 4 alleles, 3 of which are recessive and are responsible for white coloring by acting on differentiation, migration, or both of melanocyte precursor cells from the neural crest during embryogenesis.[23] The extreme white piebald allele s^w is seen in Dalmatians, Bull Terriers and English Setters,[23] whereas the s^i allele produces Irish spotting and is responsible for white pigmentation in Bloodhounds; the Beagle is usually homozygous for the piebald spotting allele s^p.[17] Data from many studies demonstrate that pigment associated deafness is the result of absent melanocytes in the stria vascularis of the cochlea, which leads to early postnatal degeneration of the stria and secondary degeneration of the cochlear hair cells and neurons.[17] For instance, in Dalmatians, a strong expression of s^w results in a reduction of melanocytes in the eye and inner ear, leading to deafness and blue eyes; weak expression of s^w results in a pigmented area, such as the patches seen in this breed.[17] However, all Border Collies are homozygous for the s^w and s^p alleles so that the *S* locus is not thought to be involved in the regulation of deafness in Border Collies.[23]

A second pigmentation locus associated with deafness is the merle locus *M*. Different dog breeds, such as the Border Collie, Dachshund, or Great Dane, are known to be heterozygous for merle (*Mm*).[23] Dogs who are homozygous for merle coat color, MM, are usually mostly white in color and, if they survive, are often deaf, blind, or both; may have ocular abnormalities, eg, microphthalmia; and are sterile.[23] For this reason, breeders tend not to breed 2 merle dogs together.

Association with Parental Hearing Status

When puppies alone were evaluated in our study, the rate of deafness was 2.2% among offspring of normal hearing dams and 10.0% among the offspring of deaf dams, suggesting an inherited mechanism exists. Although there were too few deaf sires to make a direct assessment of the sire's hearing status, the rate of deafness was higher among the offspring of untested sires, some of whom could have been deaf, than among the offspring of normal hearing sires. These results indicate that the prevalence of deafness could be reduced by selective breeding by using only those dams and sires that have been tested and found to have normal hearing.

Further evidence for an inherited component to deafness in Border Collies was provided by the generalized logistic regression modeling: the odds of deafness were found to increase by a factor of 14 for dogs with a deaf dam and 6 for dogs with an untested dam compared with the offspring of a tested normal dam. These estimates represent the residual association after adjustment for clustering within litters and for phenotypic markers of coat and iris color. This suggests that either there is incomplete penetrance of the coat/iris color gene(s) or that there are additional genes not associated with phenotypic color variants that may contribute to deafness.

For most dog breeds affected with congenital deafness, the mode of inheritance has not been established, although progress has been made for some breeds where, unlike for the Border Collie, deafness is thought to be regulated by the piebald gene. For example, strong evidence for a simple recessive mechanism has been provided for Doberman Pinschers.[25]

Several studies have demonstrated that congenital deafness is inherited in Dalmatians, but the exact mechanism is controversial.[9,23] Neither a dominant nor a recessive simple Mendelian mode of transmission could be proven by pedigree analysis.[9,23] Other hypotheses on inheritance have included a model of 2 interacting recessive loci with incomplete penetrance[5] and polygenic determination.[11] Subsequently, it was suggested that a major single recessive gene may play an important role in the transmission of deafness, but inheritance of the disease could not be completely explained.[9] Recently, it was demonstrated that a significant proportion of cases of congenital deafness can be associated with a major recessive gene not linked with eye or coat pigmentation.[15] Quite how deafness is transmitted in Border Collies is unknown at present but is under investigation by the authors.

Prevalence Estimates

The preliminary analyses, including estimation of prevalence and contingency table analysis of associations between deafness and phenotypic attributes, were based on the assumption of statistical independence between tested dogs in the same litter with respect to their hearing status. Although the genetic similarity between dogs in the same litter runs counter to this assumption, these results are of value for comparison with studies in other breeds that also did not account for litter effects.[5,13,17] However, by assuming independence within litters, these preliminary analyses may have underestimated the standard errors of the prevalence estimates and resulted in the false detection of phenotypic associations with deafness. To address these limitations and ensure that the analysis was valid, we repeated the prevalence estimation and analysis of phenotypic associations by using generalized logistic regression models that accounted for the possible clustering of deafness by litter. This approach is gaining acceptance in the veterinary research community and has been used in a similar study of deafness in the UK population of Dalmatians.[8]

In general, the analyses based on the generalized logistic regression model yielded prevalence estimates that were considerably lower than the preliminary estimates. For example, the overall prevalence estimate from the generalized logistic regression analysis was 1.6% (95% confidence interval of 0.7–2.6%) compared with the preliminary estimate of 2.8%. However, conclusions about the associations between phenotypic attributes and the prevalence of deafness remain largely unchanged. In particular, the generalized logistic regression results emphasize the high risk of deafness for Border Collies with a merle coat (prevalence of 7.9%, upper 95% confidence limit of 13.3%), blue eyes (prevalence of 9.3% for 1 blue eye and 23.9% for 2 blue eyes; corresponding upper 95% confidence limits of 15.7% and 40.0%, respectively) or excess white on the head (prevalence of 36.3%, upper 95% confidence limit of 55.3%). The prevalence estimates for Border Collies with an untested or deaf dam of 2.5 and 8.1%, respectively (with corresponding upper 95% confidence limits of 4.4 and 18.0%), provide support for a strategy of breeding only from tested normal dams.

Footnotes

[a] Domitor, Pfizer Animal Health, Kent, UK
[b] Torbugesic, Fort Dodge Animal Health, Southampton, UK
[c] Antisedan, Pfizer Animal Health, Kent, UK
[d] Sapphire 2ME, Medelec, Oxon, UK
[e] Model TDH49P, Medelec, Oxon, UK
[f] SAS/STAT software, version 8.0, SAS Institute Inc, Cary, NC

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